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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 43/00, 31/195		A1	(11) International Publication Number: WO 91/16075
			(43) International Publication Date: 31 October 1991 (31.10.91)
(21) International Application Number: PCT/AU91/00155			(74) Agent: GRIFFITH HACK & CO.: G.P.O. Box 4164, Sydney, NSW 2001 (AU).
(22) International Filing Date: 19 April 1991 (19.04.91)			
(30) Priority data: PJ 9726 20 April 1990 (20.04.90) AU			(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.
(71) Applicant (for all designated States except US): AUSTRALIAN NUCLEAR SCIENCE & TECHNOLOGY ORGANISATION [AU/AU]; Lucas Heights, NSW 2234 (AU).			
(72) Inventors; and (75) Inventors/Applicants (for US only) : TURNER, Harvey, J. [AU/AU]; Department of Nuclear Medicine, Fremantle Hospital, P.O. Box 480, Fremantle, W.A. 6160 (AU). CLARINGBOLD, Phillip, G. [AU/AU]; Department of Oncology, Fremantle Hospital, P.O. Box 480, Fremantle, W.A. 6160 (AU).			Published With international search report.
(54) Title: BONE MARROW TREATMENTS			
(57) Abstract			
<p>Haematological malignancy in an animal is treated by using a polyvalent particle-emitting radionuclide to label a bone-localising chelating agent and administering this agent to affect bone marrow of the animal, but in a dosage close to but less than a level which will cause complete bone marrow ablation, and administering a cytotoxic pharmaceutical in a dose sufficient to affect bone marrow of the animal, but also in a dose close to but less than a level which will cause complete bone marrow ablation. Examples include the use of samarium-153 as the radionuclide and a radio pharmaceutical selected from EDTMP, DTPMP, HEEDTMP, NTMP, TTHMP, HEDP and physiologically acceptable salts thereof. The cytotoxic drug can be melphalan or a derivative or analogue thereof.</p>			

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BONE MARROW TREATMENTS

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The present invention relates to bone marrow treatments, and more particularly, is concerned with a treatment in which ablation of bone marrow is achieved followed by bone marrow transplantation.

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Such treatment is possible and can be a cure for many patients with haematological malignancy such as acute leukaemia and multiple myeloma. It has been found necessary to kill all bone marrow cells. This would be fatal to the patient but for subsequent bone marrow transplantation with healthy bone marrow. If less than all the bone marrow cells are ablated, then natural recovery mechanisms operate through cell regeneration and recurrence of malignancy is likely. Thus, the patient will only enjoy a period of remission. One established technique is to achieve bone marrow ablation with total body irradiation (T.B.I.). Bone marrow transplantation with healthy bone marrow can then take place almost immediately.

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It has also been proposed to use chemoradiotherapy techniques to eradicate the haematological malignancy and this treatment immunosuppresses the patient to prevent rejection of the transplanted marrow. However, a significant proportion of patients experience life threatening or fatal non-haematopoietic toxicity, and furthermore, it appears that the procedures are not sufficiently tumoricidal to ensure ablation of a haematological malignancy and neither are the regimens sufficiently immunosuppressive to ensure marrow graft acceptance.

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It is also known to use chemotherapy treatment without radiotherapy generally using a combination of drugs with non-additive toxicities except on bone marrow. Common combination regimens usually include non-cross resistant

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agents with different spectra of antitumour activity, such as nitrosoureas (BCNU), epipodophylotoxins (VP-16) and alkylating agents (thiotepa, cyclophosphamide or melphalan). Melphalan is a drug which has been used alone
5 for attempts at bone marrow ablation. However, for multiple myeloma the success rate is very low for achieving complete clearance of the myeloma and there is significant morbidity and mortality.

Accordingly, it would be desirable to provide a
10 regimen which involves less risk to the patient of life-threatening or fatal conditions and to develop a regimen which would have a high probability of achieving successful cure and not merely a remission.

The present invention is based on the concept of
15 using a radiopharmaceutical comprising a polyvalent particle-emitting radionuclide and a chelating agent which has strong localisation on bone, the irradiation being less than the level which would be fatal in the absence of further treatment steps; administering a cytotoxic compound
20 which affects bone marrow but at a dosage less than that would be fatal in the absence of other treatment; and after allowing for the effects of the radionuclide and cytotoxic compound to dissipate, effecting a bone marrow transplantation.

25 In one aspect, the invention manifests itself in a method of treatment of an animal such as a human being, and in another aspect, manifests itself in a treatment kit for the procedure.

Preferably, the radiation emits principally beta
30 radiation which is short range but highly effective for cell ablation.

One convenient beta-emitting radionuclide is samarium-153 but there are many other possible radionuclides such as strontium-89, yttrium-90, ruthenium-103, indium-115,
35 cerium-144, gadolinium-159, holmium-166, ytterbium-175, lutecium-177, and rhenium-186.

The selection of chelating agent preferably involves a

selection of one which can be labelled with strong attachment by the radionuclide, and the resulting complex should be highly specific to bone. For example, polyaminepolyalkylphosphonic acids and derivatives including physiological salts thereof can be selected with advantage. An important example of such a compound is ethylenediaminetetramethylene phosphonate (EDTMP) which is a known chelating agent and is readily labelled with samarium-153 and has been found to localise on the surface of cortical and trabecular bone. Other chelating agents in this class are:

diethylenetriaminepentamethylenephosphonic acid (DTPMP),
hydroxyethylethylenediaminetrimethylenephosphonic acid (HEEDTMP),
nitrilotrimethylenephosphonic acid (NTMP),
tris(2-aminoethyl)aminehexamethylenephosphonic acid (TTHMP),
HEDP, or
physiologically acceptable salts of any one of these compounds.

The choice of cytotoxic compound includes melphalan (described in U.S. patent Nos. 3,032,584 and 3,032,585) and related compounds including equivalent chemotherapeutic agent with a predominantly myelotoxic action.

A preferred embodiment of the invention comprises the use of EDTMP labelled with samarium-153 administered at a high but sub-lethal level. However, it is thought that although samarium-153 labelled EDTMP is myelosuppressive, complete marrow ablation is not achieved even with very high dosage levels. Attempts to produce complete marrow ablation in dogs and rabbits have been reported as not successful, and further studies by the present inventor indicate that in rats samarium-153 EDTMP alone is unlikely to completely ablate red marrow.

Another embodiment consists in the use of rhenium-186

labelled HEDP.

Preferably, the treatment comprises delaying administration of the cytotoxic drug for several days to allow substantial radioactive decay of the radiopharmaceutical.

For illustration purposes only, reference will be now made to the accompanying drawings which illustrate trials in rats.

Referring first to Figure 1, the graph illustrates platelet concentration in the blood with time following a lethal total body irradiation in rats. The irradiation caused marrow ablation and the non-irradiated control example of rats (7 in number) maintained a substantially constant platelet concentration in blood. The irradiated sample of 5 rats showed a decline in platelet concentration in accordance with the normal decline of platelet concentration in the absence of fresh platelet generation by marrow. This model established the validity of monitoring platelet concentration as an indicator of bone marrow ablation.

Figure 2 demonstrates the viability of marrow transplantation after total body irradiation, i.e. marrow ablation. The control sample with no marrow transplantation showed all rats died within about 10 days but a very high survival rate was achieved with those that received marrow transplantation.

Figure 3 is a graph of platelet concentration with time. A lethal total body irradiation is given to the sample and marrow transplantation effected. By day 10, platelet concentration had dropped to a potentially fatal level. However, the increase in platelet concentration demonstrated that the transplantation had been effective and bone marrow cell reproduction had occurred to rescue the animals and a normal platelet concentration was achieved by day 15.

Figure 4 demonstrates the use of samarium-153 EDTMP at a rate of 3.5 GBq instead of total body irradiation.

Samarium-153 EDTMP was prepared according to published methods (Turner et al 1989 Eur.J.Nucl.Med.15: 784-795). Briefly, Samarium-153 was prepared by neutron irradiation of Sm_2O_3 (enriched to 98% Samarium-152) in the HIFAR Research Reactor, Australian Nuclear Science and Technology Organisation, using a thermal flux of $5 \times 10^{13} \text{ ncm}^{-2} \text{ s}^{-1}$. Samarium-153 was supplied as a sterile solution of $^{153}\text{Sm Cl}_3$ in physiological saline and was added to a lyophilized EDTMP kit immediately prior to use. Again the control sample had a steady platelet concentration but the irradiated sample showed that although the platelet concentration had dropped close to the level at which the animal's life is threatened, spontaneous recovery occurred and this is thought to be due to the fact that the samarium-153 EDTMP may not cause complete marrow ablation.

Referring now to Figure 5, the effect on rats of melphalan at varying dose rates is indicated. It is only when dosages of around 9 mg/kg are given that survival is threatened, but then a precipitous result is observed. On this basis, in rats, a dose of about 9.5 mg/kg would be close to the fatal dose for most individuals.

Figure 6 demonstrates survival rate after chemo- and/or radiotherapy treatment comprising 9.5 mg/kg Melphalan and samarium-153 EDTMP administered at 555mBq.

A control with melphalan alone indicated 100% survival. A sample comprising the samarium and melphalan but without marrow transplantation produced a low survival rate of about 20%. The third line demonstrates a sample of 13 individuals treated with samarium-153, melphalan, and given a marrow transplant at day 3, and again a survival rate of about 20% only was achieved. This result indicates that the transplantation was not successful due to the half-life of the radionuclide, and marrow transplantation needs to be delayed until the effects of the internal endoradiotherapy have diminished.

Figure 7 indicates the result of delaying marrow transplant until six days after the commencement of the

procedure. In this case, the procedure commenced with samarium endoradiotherapy, and five days later the cytotoxic compound melphalan was administered. On day six, marrow transplantation occurred, and in the control sample which
5 did not receive the transplantation, the survival rate was approximately 20% whereas for those individuals receiving the transplant the survival rate exceeded 90%.

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CLAIMS

1. A pharmaceutical comprising a supply of bone-localising chelating agent, a supply of polyvalent particle-emitting radionuclide for labelling the chelating agent, and a cytotoxic drug, the radionuclide and cytotoxic drug being in a dosage which when administered in combination will cause bone marrow ablation in animals, each dosage being close to but less than a level which will cause complete bone marrow ablation.
2. A pharmaceutical as claimed in claim 1, wherein the radionuclide is selected from the group consisting of samarium-153, strontium-89, yttrium-90, ruthenium-103, indium-115, cerium-144, gadolinium-159, holmium-166, ytterbium-175, lutecium-177, and rhenium-186.
3. A pharmaceutical as claimed in claim 1 or claim 2 wherein the radiopharmaceutical is selected from EDTMP, DTPMP, HEEDTMP, NTMP, TTHMP, HEDP and physiologically acceptable salts thereof.
4. A pharmaceutical as claimed in any one claims 1 to 3 and wherein the cytotoxic drug is melphalan or a derivative or analogue thereof, or a chemotherapeutic agent with a predominantly myelotoxic action and substantially equivalent to melphalan.
5. A method of treating haematological malignancy in an animal being comprising administering a bone-localising radiopharmaceutical labelled with a polyvalent particle-emitting radionuclide to affect substantially bone marrow of the animal, administering a cytotoxic pharmaceutical in a dose sufficient to affect substantially bone marrow of the animal, the combined doses of the radio pharmaceutical and the cytotoxic pharmaceutical being chosen to cause bone marrow ablation, after a delay sufficient to allow substantial decay of the radiopharmaceutical, effecting a bone marrow transplantation.

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- 8 -

6. A method as in claim 5 wherein the radiopharmaceutical is labelled with a radionuclide selected from the group consisting of samarium-153, strontium-89, yttrium-90, ruthenium-103, indium-115, cerium-144, gadolinium-159, holmium-166, ytterbium-175, lutecium-177, and rhenium-186.

7. A method as in claim 5 or claim 6, wherein the radiopharmaceutical is selected from EDTMP, DTPMP, HEEDTMP, NTMP, TTHMP, HEDP and physiologically acceptable salts thereof.

8. A method as in any one of the claims 5 to 7 wherein the cytotoxic drug is melphalan or a derivative or analogue thereof or a chemotherapeutic agent with a predominantly myelotoxic action and substantially equivalent to melphalan.

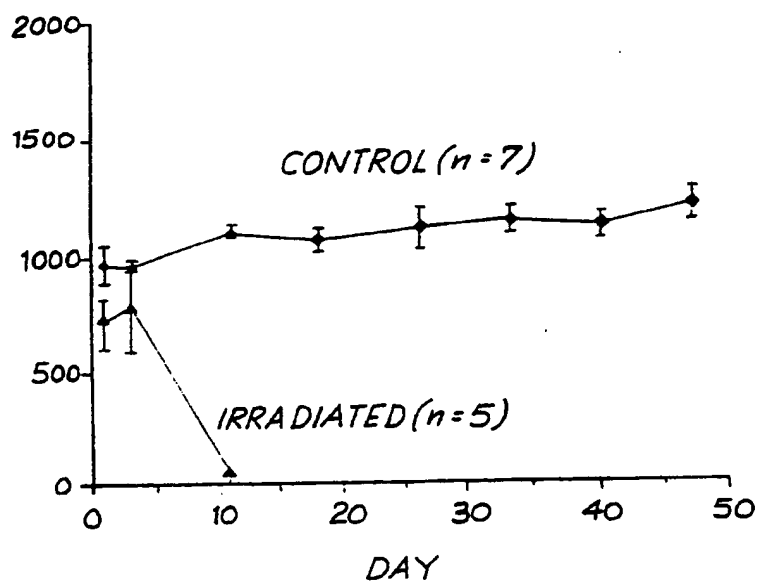
9. A method as in any one of claims 5 to 8 wherein the cytotoxic drug is administered a few days after the radiopharmaceutical, and the bone marrow transplantation is delayed of the order of a day after administering the cytotoxic drug.

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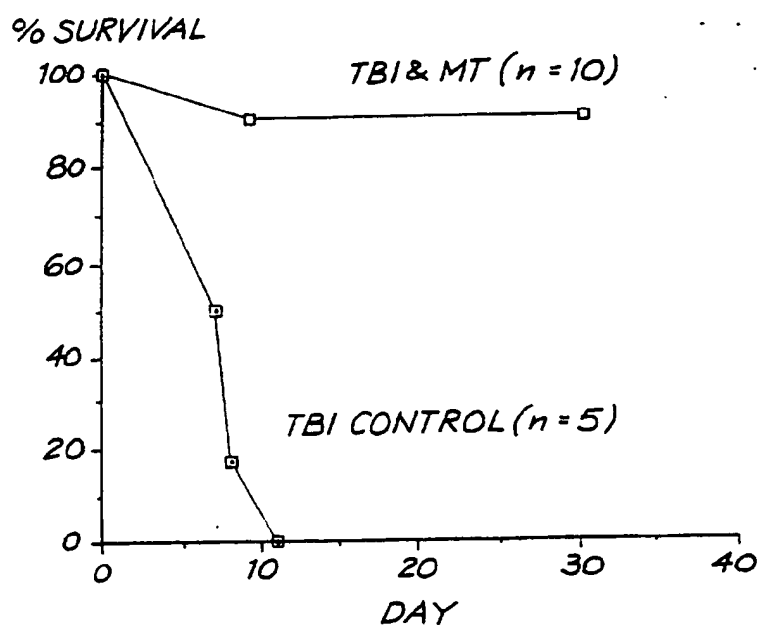
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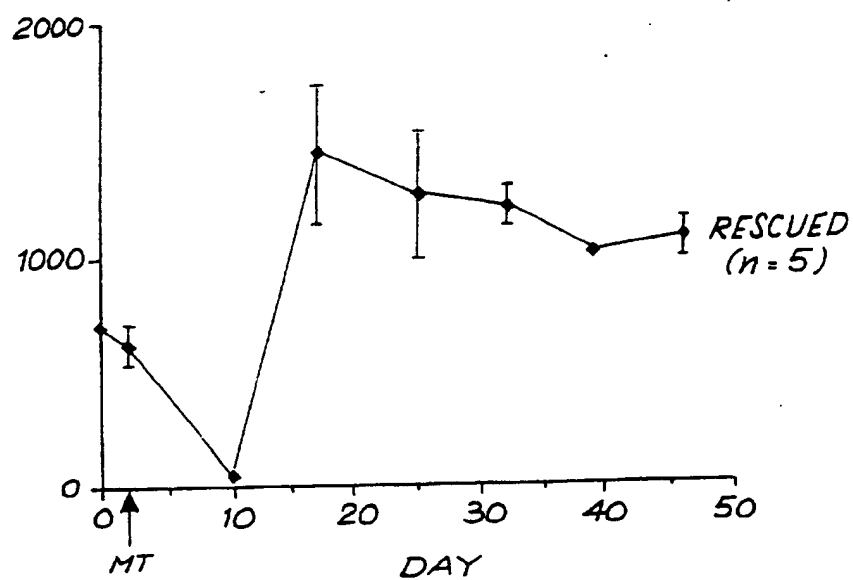
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*LETHAL TOTAL BODY IRRADIATION IN WAG RATS**PLATELET CONC. ($\times 10^9/L$)**FIG. 1*

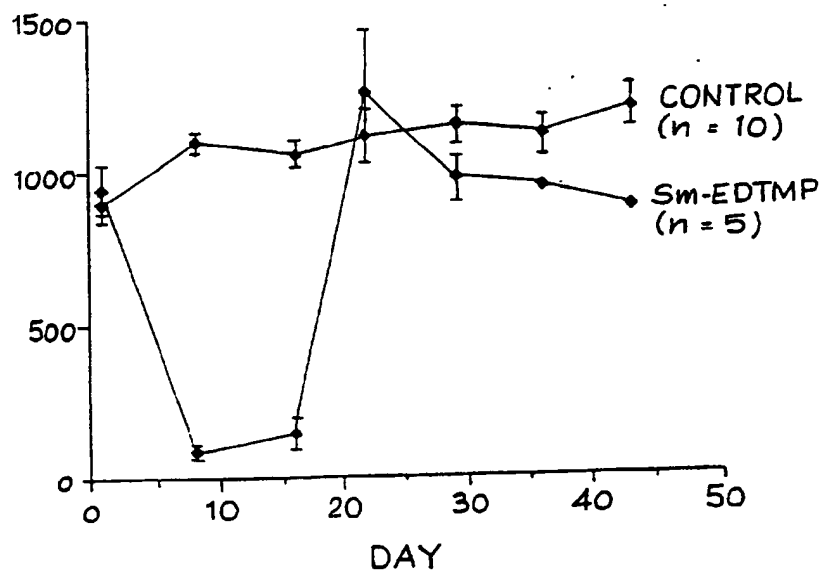
2/7

SURVIVAL AFTER TBI & MARROW TRANSPLANTATION**FIG. 2****SUBSTITUTE SHEET**

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*MARROW TRANSPLANTATION AFTER LETHAL TBI**PLATELET CONC. ($\times 10^9/L$)**FIG. 3***SUBSTITUTE SHEET**

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*IRRADIATION BY SAMARIUM-153-EDTMP: 3.5 GBq IV.**PLATELET CONC. ($\times 10^9/L$)***FIG. 4**

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SURVIVAL AFTER 0.5 -10.0 mg/kg MELPHALAN IP.

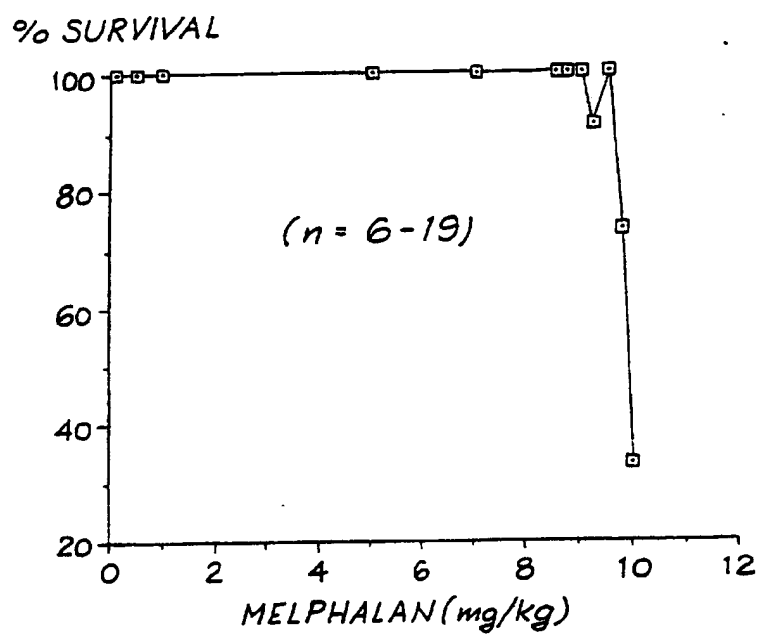
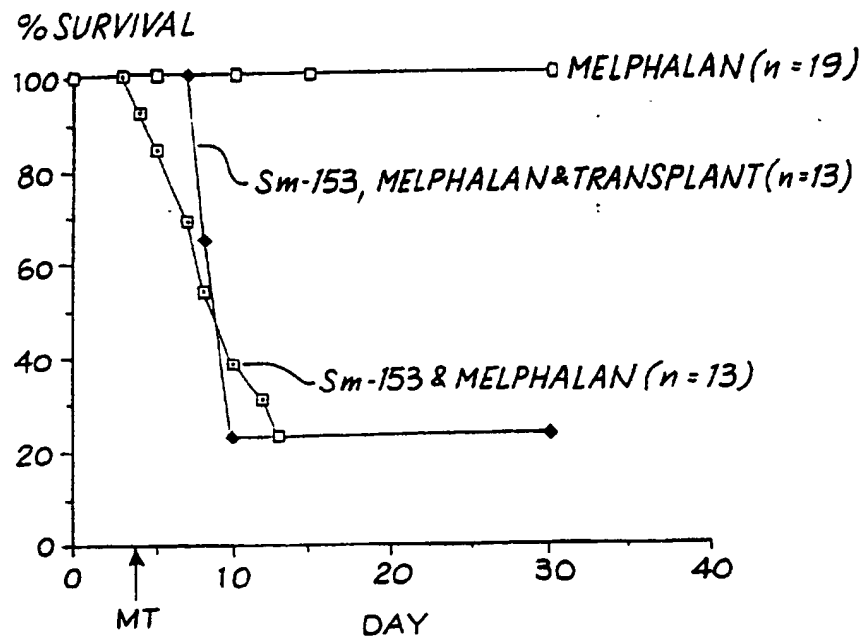


FIG. 5

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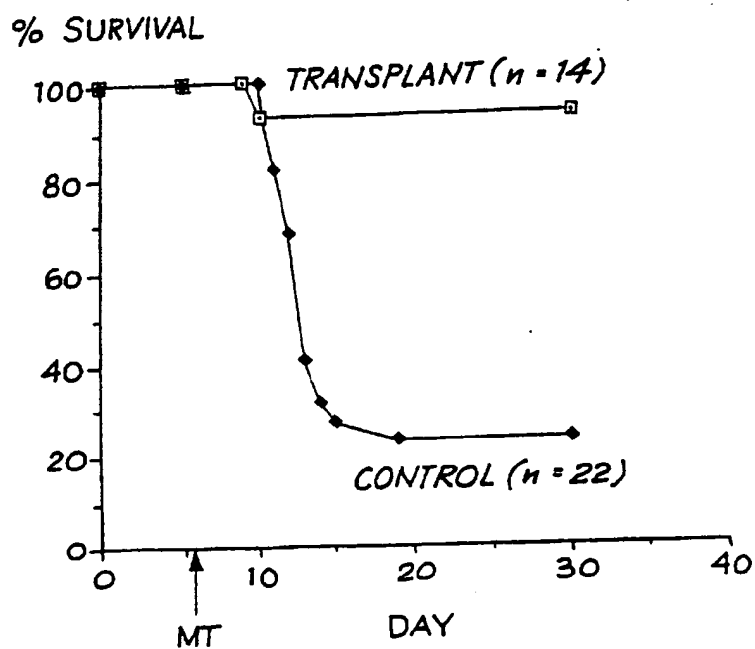
SURVIVAL AFTER CHEMORADIO THERAPY:
9.5mg/kg MELPHALAN and 555 mBq/kg ^{153}Sm -EDTMP

**FIG. 6****SUBSTITUTE SHEET**

7/7

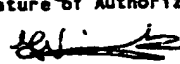
SURVIVAL AFTER SEQUENTIAL CHEMORADIO THERAPY:

555 mBq/kg ^{153}Sm EDTMP	DAY 0
9.5 mg/kg MELPHALAN	" 5
MARROW TRANSPLANTATION	" 6

**FIG. 7****SUBSTITUTE SHEET**

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/AU 91/00155**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. ⁵ A61K 43/00, A61K 31/195		
II. FIELDS SEARCHED		
Minimum Documentation Searched 7		
Classification System	Classification Symbols	
IPC	A61K 43/00, A61K 31/195	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8		
AU : IPC as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT 9		
Category*	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	US,A, 4853209 (KAPLAN et al.) 1 August 1989 (01.08.89) See entire document, claims 1,9,11,12,17,18.	(1-9)
X	US,A, 4882142 (SIMON et al.) 21 November 1989 (21.11.89) See entire document, claims 1,5,7,8,13,14.	(1-9)
X,P	US,A, 4976950 (SIMON et al.) 11 December 1990 (11.12.90) See entire document, claims 1,3,5,6,7,10.	(1-9)
A	EP,A, 164843 (THE DOW CHEMICAL COMPANY) 18 December 1985 (18.12.85) See claim 1.	(1-3)
A,P	EP,A, 375376 (THE DOW CHEMICAL COMPANY) 27 June 1990 (27.06.90) See claim 1.	(1-3)
(continued)		
<p>* Special categories of cited documents: 10</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
2 August 1991 (02.08.91)	13 August 91	
International Searching Authority	Signature of Authorized Officer	
Australian Patent Office	 TAMARA NIZNIK	

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US,A, 3965254 (TOFE et al.) 22 June 1976 (22.06.76) See entire document, column 9 lines 36-68.	(1-4)
A	'Goodman and Gilman's The Pharmacological Basis of Therapeutics' eds A.G. Gilman et al., seventh edition, published 1985, by Macmillan Publishing Company (New York) see page 1243.	(1-9)

V. [] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2. [] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1. [] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [] The additional search fees were accompanied by applicant's protest.
 [] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (supplemental sheet (2)) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 91/00155

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Patent Document Cited in Search Report		Patent Family Members			
US	4853209	AU 80453/87	DK 5706/87	EP	291605
		JP 63287729	NZ 222304	PT	86020
		ZA 8708169			
US	4882142	AU 45440/89			
US	4976950	DK 5827/89			
		EP 374501			
		JP 2237936			
EP	164843	AU 41229/85	CA 1243603	IL	74902
		JP 61022029	NZ 211808	ZA	8502799
		US 4898724			
EP	375376	AU 47009/89	AU 48282/90	BR	8907255
		CN 1046739	DK 1959/90	EP	408701
		HU 54897	NO 903632	WO	9006776
US	3965254	AU 69210/74	BE 815397	CA	1028246
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		NL 7406952	PH 12898	ZA	7403159

END OF ANNEX

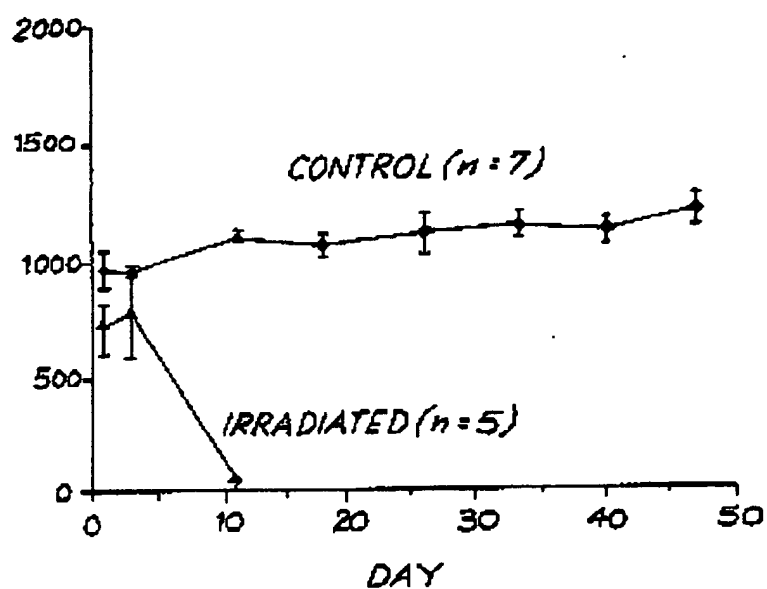
ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 91/00155

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Patent Document Cited in Search Report		Patent Family Members			
US	4853209	AU	80453/87	DK	5706/87
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				PH	12898

END OF ANNEX

1/7

LETHAL TOTAL BODY IRRADIATION IN WAG RATSPLATELET CONC. ($\times 10^9/L$)**FIG. 1**

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SURVIVAL AFTER TBI & MARROW TRANSPLANTATION

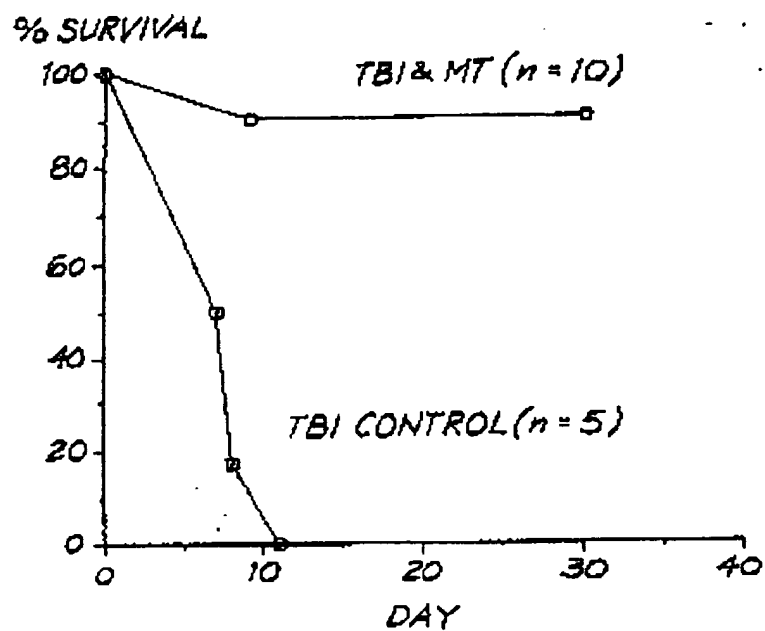
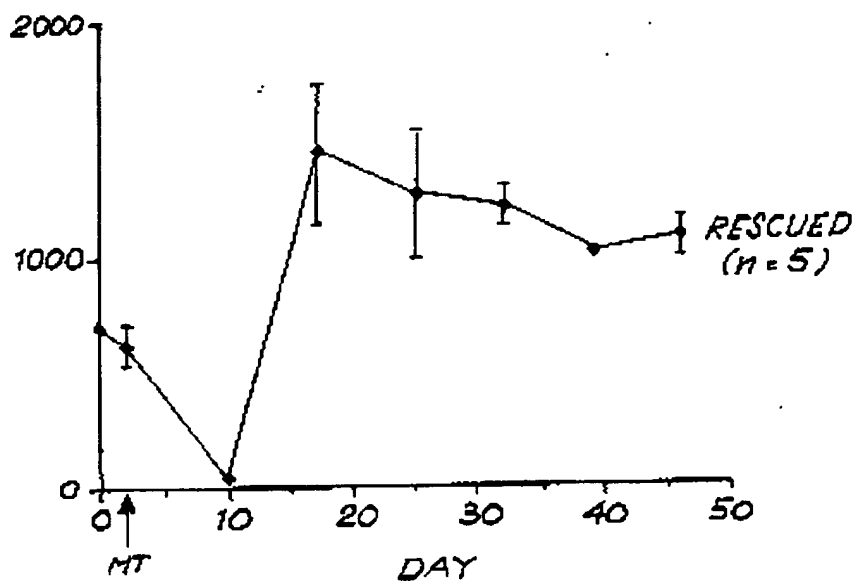


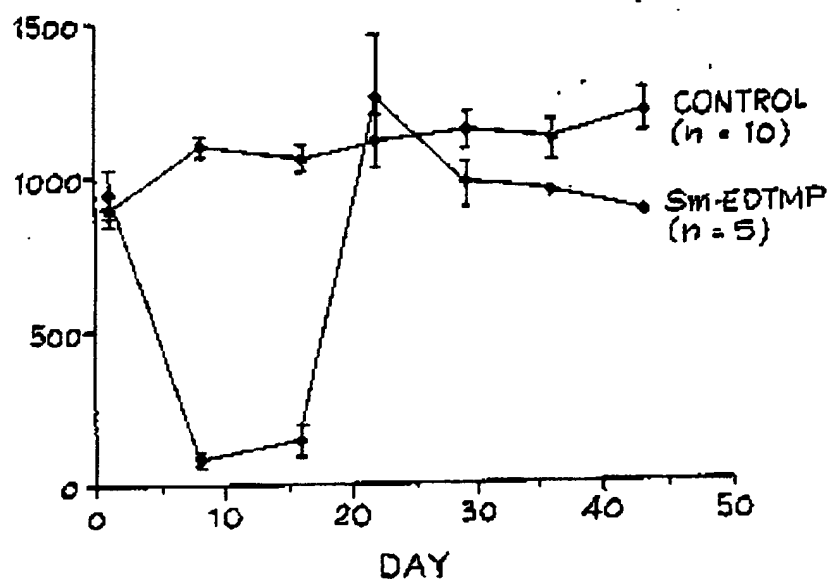
FIG. 2

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MARROW TRANSPLANTATION AFTER LETHAL TBIPLATELET CONC. ($\times 10^9/L$)**FIG. 3****SUBSTITUTE SHEET**

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*IRRADIATION BY SAMARIUM-153-EDTMP: 3.5 GBq IV.**PLATELET CONC. ($\times 10^9/L$)***FIG. 4**

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SURVIVAL AFTER 0.5-10.0 mg/kg MELPHALAN IP.

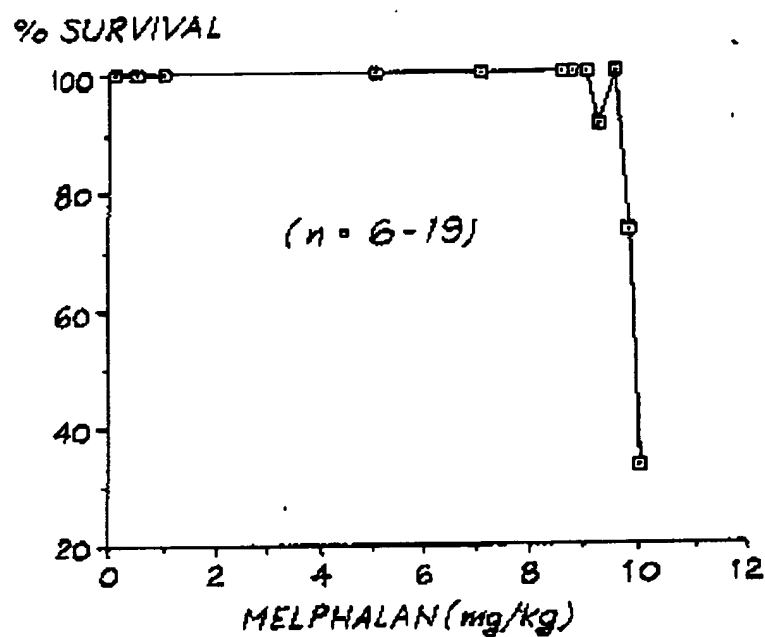


FIG. 5

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SURVIVAL AFTER CHEMORADIO THERAPY:
9.5mg/kg MELPHALAN and 555 mBq/kg ^{153}Sm -EDTMP

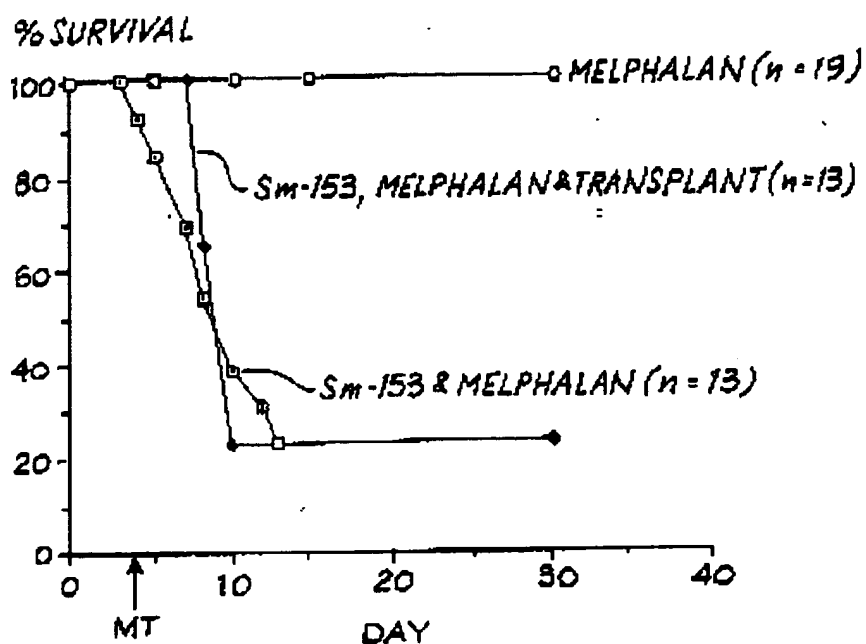


FIG. 6

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SURVIVAL AFTER SEQUENTIAL CHEMORADIO THERAPY:

555 mBq/kg ^{153}Sm EDTMP	DAY 0
9.5 mg/kg MELPHALAN	" 5
MARROW TRANSPLANTATION	" 6

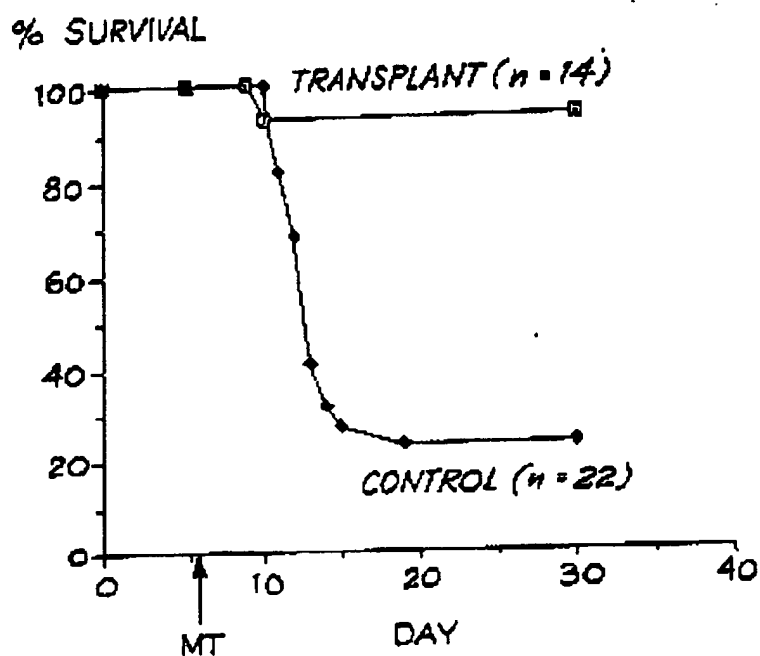


FIG. 7

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